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PAPER

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Meyer–Schuster rearrangement of propargylic alcohols mediated by phosphorus-containing Brønsted acid catalysts†

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Commercially available (aqueous) hypophosphorus acid is an efficient catalyst for the synthesis of α,β-unsaturated carbonyl compounds from their corresponding propargylic alcohols. Reactions were carried out in technical toluene in the presence of air and in several instances the desired products were isolated analytically pure after a simple work-up.

Introduction

Propargylic alcohols are popular intermediates due to their easy preparation and versatile reactivity. They are the obvious precursors for a range of propargylic moieties occurring in natural products and synthetic pharmaceuticals, and their rearrangement produces α,β-unsaturated carbonyl compounds, equally desirable compounds. This rich reactivity is not without its caveats since often promoting a specific transformation over other available pathways remains a challenge.

The Meyer–Schuster rearrangement was originally reported in a range of acidic media such as acetic acid, acetyl chloride and concentrated sulfuric acid, and related Rupe isomerisation is competitive when the starting alcohol contains any beta-hydrogens, leading to an alternative enone as the final product (Scheme 1).[1,2] The use of strong acids and high temperatures for accessing the key carbocationic intermediates hampered the early widespread application of these powerful rearrangements. In consequence, the alternative activation of the alkyne by a range of soft Lewis acids/transition metal catalysts is now well established for Meyer–Schuster rearrangement.[3,4]

These recent developments typically involve mild reaction conditions, but some issues remain, including cost effectiveness since ruthenium and gold-based catalysts are arguably the most popular options. Therefore, it is not surprising that efforts towards reliable Brønsted acid-based catalytic systems for Meyer–Schuster rearrangements are still ongoing.[5,6] For instance, the level of stereocontrol of the desired unsaturated products by either heteropoly acids,[7] or tailored boronic acids[8]

is truly remarkable.[9] Alternatively, recent reports on simple and economical Brønsted acids such as phosphorous acid or *p*-toluenesulfonic acid address some of the classic limitations of these isomerisations, still they present clear limitations. PTSA can stereoselectively promote the Meyer–Schuster rearrangement of secondary propargylic alcohols but the reaction is limited to terminal alkynes and 30 mol% acid in hot dichloroethane (cancerogenic) are required.[10] On the other hand, 1.5 equivalents of phosphorous acid $(OH)_2P(O)H$ were needed to isomerise a range of mono- and disubstituted hydroxyalkynes in an overpressured vessel under inert atmosphere.[11] In our previous studies on nucleophilic substitutions of propargylic alcohols with either HBF_4[12] or diethylphosphite[13] as catalysts we occasionally noticed the formation of rearrangement by-products. Capitalising on these observations, we herein report our efforts to develop an economical, readily accessible and user friendly methodology for Meyer–Schuster reactions.
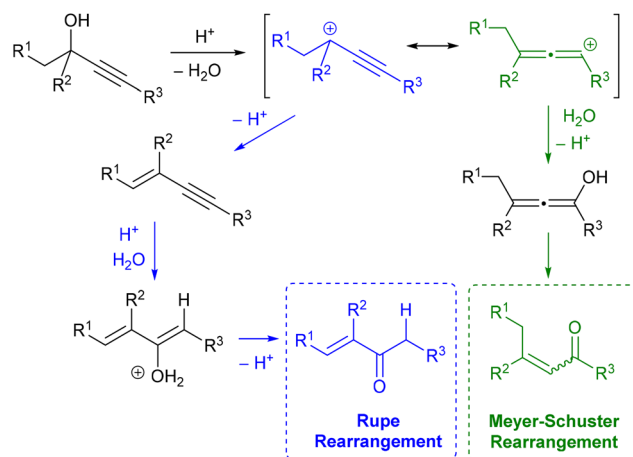
Scheme 1 The Meyer–Schuster and Rupe rearrangements.

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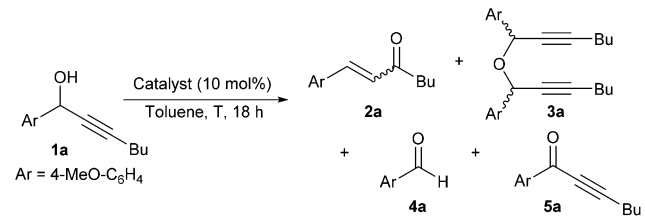
Results and discussion

Commercially available phosphorus-based acids were tested in technical toluene at 90 °C in the presence of air with **1a** as model substrate to obtain enone **2a** (Table 1). No starting alcohol was recovered in any of these reactions and while trace amounts of aldehyde **4a** and ketone **5a** were formed in most tests, the main by-product in these reactions was ether **3a**, issue of a condensation reaction of the starting propargylic alcohol. While a reasonable NMR yield of 60% was achieved with phosphorous acid (Table 1, entry 2), diethyl phosphite and aqueous hypophosphorous acid gave the highest conver-

sions in enone **2a** with high and complete selectivity, respectively (Table 1, entries 3 and 5). In comparison, significant decomposition was observed with polyprotic acids and diphenyl phosphate (Table 1, entries 1, 2 and 4). Overall, there was no correlation between the catalyst pK_a and the yield in enone **2a**, and aqueous hypophosphorous acid was chosen as the optimal catalyst due to its lower price per mol.[14] Temperatures lower than 90 °C reduced the conversion and E/Z selectivity for enone **2a**, as well as increased product decomposition and formation of ether **3a** (Table 1, entries 5–7).

Alternative solvents were then screened with the model substrate but none of the apolar or polar solvents tested could match toluene in terms of reactivity or selectivity (Table 2, entries 1–5). No by-products issue of a Friedel-Craft reaction of toluene were observed in any of these reactions, while lower acid loadings reduced the NMR yields for **2a** even if no starting alcohol was recovered. On the other hand, the stereoselectivity remained very high in all cases (Table 2, entries 1 and 6–8).

The ^{31}P NMR of the commercial aqueous solution used as catalyst in $CDCl_3$ displays two triplets, a sharp one at 12.1 ppm and a broad one at 12.5 ppm with respect to H_3PO_4 as external reference ($^{1}J_{PH}$ = 568 Hz). This supports tetrahedral hypophosphorous acid (or phosphinic acid) as the major tautomer with respect to less stable trigonal pyramidal phosphonous acid as well as a significant dimerisation in solution through hydrogen bonding (Scheme 2).[15] Similar spectra were obtained in toluene-d8.[16] When enone **2a** was prepared under the optimised conditions no hypophosphorous acid was detected at the end of the reaction, but phosphorous acid (*ca.* 12%)[17] was identified in the reaction crude. This indicates that while phosphorous acid can catalyse this rearrangement, hypophosphorous acid eventually disproportionates into phosphorous acid at the reaction temperature,[18] which would then increase the percentage of decomposition of the reaction mixture (see Table 1, entry 2).[15] Nevertheless, the bulk of the signals in ^{31}P NMR appeared in the 25–70 ppm region, which is characteristic
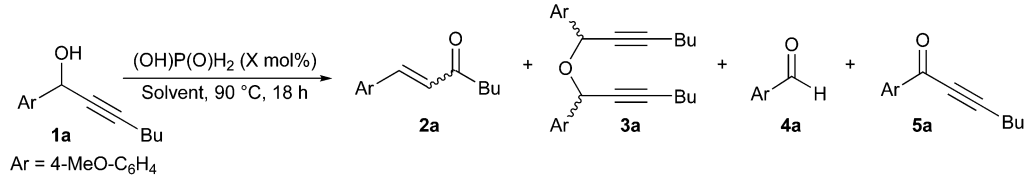
Table 1 Catalyst screening[a]

Entry	Catalyst	T (°C)	$2a^b$ (%)	$E:Z^b$	$3a^b$ (%)	$4a^b$ (%)	$5a^b$ (%)
1^c	aq. $(OH)_3P(O)$	90	31	94:6	<5	<5	5
2	$(OH)_2P(O)H$	90	60	97:3	<5	<5	<5
3	$(OH)P(OEt)_2$	90	84	95:5	—	<5	5
4	$(OH)P(O)(OPh)_2$	90	19	83:17	17	<5	—
5^d	aq. $(OH)P(O)H_2$	90	90	E only	<5	<5	5
6^d	aq. $(OH)P(O)H_2$	70	63	64:36	<5	<5	<5
7^d	aq. $(OH)P(O)H_2$	50	11	30:70	53	<5	<5

[a] Reaction conditions: **1a** (1 mmol), catalyst (10 mol%) in technical toluene (1 mL), T (°C), 18 h. [b] ^1H NMR yields and ratios were calculated using dibromomethane as internal standard and are the average of at least two independent experiments. [c] 85 wt% aqueous solution. [d] 50 wt% aqueous solution.

Table 2 Further optimisation[a]

Entry	Solvent	Cat. (mol%)	$2a^b$ (%)	$E:Z^b$	$3a^b$ (%)	$4a^b$ (%)	$5a^b$ (%)
1	Toluene	10	90 (95)^c	E only	<5	<5	5
2	Cyclohexane	10	68	97:3	—	<5	—
3	1,2-Dioxane	10	67	86:14	—	<5	5
4	2-Me-THF	10	52	80:20	—	<5	5
5	Acetonitrile	10	47	88:12	—	<5	<5
6	Toluene	5	71	97:3	<5	<5	<5
7	Toluene	2.5	68	97:3	<5	<5	<5
8	Toluene	1	65	96:4	<5	<5	<5

[a] Reaction conditions: **1a** (1 mmol), aq. $(OH)P(O)H_2$ (X mol%) in technical solvent (1 mL), 90 °C, 18 h. [b] ^1H NMR yields and ratios were calculated using dibromomethane as internal standard and are the average of at least two independent experiments. [c] Isolated yield.
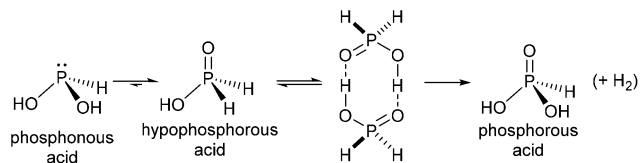
Scheme 2 Phosphorous species in Meyer–Schuster rearrangement reactions.

of R_3PO derivatives. Either $(OH)P(O)H_2$ and/or $(OH)_2P(O)H$ might act as nucleophiles producing either propargylic or allenic H-phosphinic acids,[19,20] however, the instability of the formed species prevented further characterisation. Comparable results were obtained when the model reaction was carried out in the presence of diethyl phosphite, the other efficient catalyst identified in the original screening (see Table 1, entry 3).

Table 3 Scope of the reaction

Entry	Rearrangement	Product	T (°C)	2^a (%)	$E:Z^b$	3^a (%)
1		2a	90	90 (95)	E only	<5
2		2b	90	91 (81)	E only	—
3		2c	90	>95 (99)	E only	—
4		2d	90	91 (91)	1:1	—
5		2e	90	55 (51)	2:1	—
6		2f	90	—	—	50
			110	—	—	8
7		2g	90	41 (34)	E only	—
8		2h	90	>95 (93)	53:47	—
9		2i	90	59	88:12	27
			110	68 (58)	E only	—
10		2j	90	44	76:24	32
			110^c	64 (69)	E only	—
11		2k	90	90 (85)	—	—
12		2l	90	11	—	—

^{a} ^{1}H NMR yields and ratios were calculated using dibromomethane as internal standard and are the average of at least two independent experiments. Isolated yields are provided in brackets. ^{b} E/Z ratios were calculated from the crude ^{1}H NMR spectra. ^{c} aq. $(OH)P(O)H_2$ (5 mol%).

With an optimised system in hand, we next explored the scope of the reaction (Table 3). A range of enones **2** was prepared in moderate to excellent yields as well as α,β-unsaturated esters and aldehydes (Table 3, entries 4–6). The reaction conditions had to be slightly modified for several substrates to minimise undesired decomposition, or formation of by-products **3**. In several instances diethyl phosphite was used as alternative catalyst in an attempt to improve the overall yield in the desired α,β-unsaturated carbonyl compounds. While similar results were obtained in most cases, no overall improvement was achieved. Only a trimethylsilyl substituent at the acetylenic position precluded the Meyer–Schuster rearrangement from taking place with ether **3f** as the only identifiable reaction product (Table 3, entry 6). Gratifyingly, many of the desired rearrangement products were isolated analytically pure after a simple aqueous work-up, and purification by column chromatography was only required for problematic substrates such as **2g**, **2j** or **2l**. Unsurprisingly, no reaction was observed with alkyl (propyl or cyclohexyl) propargylic alcohols.

While bis-aryl propargylic alcohol **1k** formed the corresponding enone in good yields, the reaction of a tertiary alcohol bearing a methyl group at the C_α position suffered from severe decomposition and the desired enone **2l** was only observed in low conversion together with traces of enyne **6l** (Table 3, entries 11, 12 and Scheme 3A). Lowering the reaction temperature to 50 °C improved the formation of **6l** so it could be isolated and fully characterised. This enyne is a known intermediate in Rupe rearrangements but the hydration of **6l** was never observed under the tested conditions, even after extended reaction times.

We were surprised by these results since we had previously isolated enone **2l** in fair yield during our studies on nucleophilic substitution reactions with diethylphosphite as catalyst, instead of the expected propargylic amine (Scheme 3B).[13] However, only traces of **2l**, if any, were observed in the absence of 4-cyanoaniline, which indicates

Table 4 Reactions of **1b** and **3b**[a]

| Entry	Starting material	Conditions	**1b**[b] (%)	**2b**[b] (%)	E : Z	**3b**[b] (%)
1	**1b**	Cat. (10 mol%), RT	22	—	—	78
2		Cat. (10 mol%), 40 °C	<5	—	—	>95
3		Cat. (10 mol%), 60 °C	<5	26	65 : 35	69 (64)
4	**3b**	Cat. (10 mol%), 60 °C	—	31	65 : 35	51
5		60 °C	—	—	—	>95

[a] Reaction conditions: **1b** (1 mmol), aq. (OH)P(O)H$_2$ (X mol%) in technical toluene (1 mL), T (°C), 24 h. [b] ^{1}H NMR yields/recoveries and ratios were calculated using dibromomethane as internal standard and are the average of at least two independent experiments. Isolated yield is provided in brackets.

that the basicity of this nucleophile is key to tame the reactivity of phosphorous acid, the most acidic phosphorous by-product observed either from diethylphosphite or hypophosphorous acid under our conditions. Indeed, the use of a suitable base might be key to avoid decomposition, particularly for substrates susceptible of undergoing competitive Rupe rearrangement.

Finally, we looked into the role of ethers **3** in these rearrangement reactions since the formation of this by-product was systematically favoured by lower reaction temperatures with our catalytic system. Indeed, ether **3b** was the only observed product from the reaction of alcohol **1b** at temperatures up to 50 °C, whereas a mixture of **2b** and **3b** was formed at 60 °C (Table 4, entries 1–3). Interestingly, similar results were obtained at 60 °C when ether **3b** was used as starting material, while no reaction was observed in the absence of acid. As expected, lower stereoselectivities were obtained at lower reaction temperatures (see Table 3, entry 2). These results confirm that ethers **3** can act as intermediates in the formation of α,β-unsaturated carbonyl compounds,[7] probably through the protonation of ether **3b** followed by the thermal cleavage into the corresponding propargylic alcohol **1b** and carbocation derivative that might then engage in a Meyer–Schuster rearrangement.

Conclusions

The preparation of α,β-unsaturated carbonyl compounds from propargylic alcohols assisted by commercially available aqueous hypophosphorous acid does not require costly metals and delivers the desired products in technical solvent without the requirement of inert atmosphere, or (in many cases) further purification after a work-up. While Brønsted acid cata-
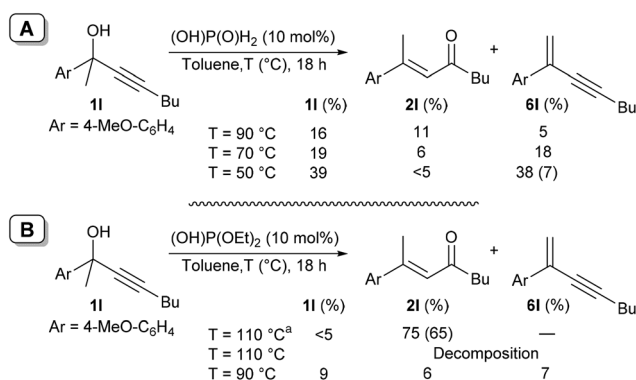
Scheme 3 Reactions of tertiary alcohol **1l**. ^{1}H NMR yields were calculated using dibromomethane as internal standard and are the average of at least two independent experiments. Isolated yields are provided in brackets. [a] Reaction carried out in the presence of 1.5 equiv. of 4-cyanoaniline.

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lysts are intrinsically limited to substrates able to form sufficiently stable carbocations, different substitution patterns on the propargylic aromatic substituent and at the acetylenic position allowed the formation of unsaturated ketones, esters and aldehydes.

These reactions are deceptively simple. While they are distinctly easy to carry out, the effects of the reaction temperature and speciation of the phosphorous catalyst are not that straightforward. Higher temperatures promote the conversion of ethers **3** into the desired unsaturated products **2** and improve the overall stereoselectivity of the reaction, nevertheless, they also lead to significant decomposition of the reaction mixture. Prolonged periods of heating in the presence of moisture and oxygen, while user-friendly, inevitably leads to the formation of different phosphorous species throughout the reaction, which might be effective catalysts as well and/or promote decomposition. A better understanding of the different roles could lead to an improved control and reactivity in this and other transformations mediated by Brønsted acids.

Experimental section

General considerations

All reactions were carried out in air using technical solvents without any particular precautions to exclude moisture or oxygen, unless stated otherwise. Commercially available reagents were used as received without further purification. Column chromatography and TLC were performed on silica gel (Kieselgel 60), using UV light and a phosphomolybdic acid dip to visualize the products.

General procedure for the Meyer–Schuster rearrangement reactions

The chosen propargylic alcohol (1.0 mmol) was added to a solution of aq. $(OH)P(O)H_2$ (50 wt% aq. solution, 5–10 mol%) in technical toluene (1.0 mL). The reaction mixture was stirred at 90–110 °C on a heating block for 18 h, before being cooled to room temperature. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. If necessary, the obtained residue was then purified by column chromatography (reaction crude was dry-loaded onto stationary phase).

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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